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Familial pericentric inversion of chromosome 5 in a family with benign neonatal convulsions

D Concolino, M A Iembo, E Rossi, S Giglio, G Coppola, E Miraglia del Giudice, P Strisciuglio

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We describe a family in whom a pericentric inversion of chromosome 5 segregates with benign familial neonatal convulsions (BFNC). BFNC is an autosomal dominant form of epilepsy characterised by spontaneous partial or generalised clonic convulsions beginning within the first months of life. Seizures usually disappear by the age of 6 months; intercritical electroencephalogram and subsequent psychomotor development are normal. BFNC loci have been mapped to human chromosomes 20q13.3 (*BFNC1*) and 8q24 (*BFNC2*), based on linkage analysis.[1 2] Recently, two potassium channel genes (*KCNQ2* and *KCNQ3*), located in these two regions, were shown to be mutated in BFNC1 and BFNC2, respectively.[3 4]

We report a family with BFNC and a pericentric inversion of chromosome 5 cosegregating with BFNC. Fluorescence in situ hybridisation (FISH) experiments were performed to define the breakpoints at YAC level. The linkage of BFNC to *KCNQ2* and mutations in the *KCNQ3* gene were excluded. This report raises the possibility of a new locus for BFNC on chromosome 5.

CASE REPORT

The proband, a male, was the second child of unrelated parents, born at 40 weeks of gestation after an uneventful pregnancy. Apgar score was 10 at one and five minutes. The parents were both 32 years old at his birth. Birth weight was 3400 g (50-75th centile), length was 51 cm (50-75th centile), head circumference was 35 cm (50-75th centile), and the clinical examination was normal except for the presence of hypotelorism. On the third day of life he had five episodes of generalised clonic convulsions treated with phenobarbital (5 mg/kg/day). Two additional episodes of seizures occurred during the first months of life and therefore long term therapy was continued. Routine laboratory investigations including plasma ammonia levels and acid base status were normal. Plasma and urinary amino acids were normal. Brain CT scan, electroencephalogram, echocardiography, and abdominal echography were all normal. At 8 months of age he was developmentally normal and continued to take phenobarbital.

The mother and maternal grandmother appeared to be intellectually normal but reported a clear history of convulsions in infancy and afebrile seizures later in childhood. Both showed hypotelorism without other clinical or dysmorphic signs. No other relatives of the proband had hypotelorism or a history of idiopathic neonatal convulsions.

Cytogenetic and molecular analysis

Chromosome analysis was performed on QFQ and GTG banded metaphases from synchronised peripheral lymphocyte cultures using standard procedures. The proband's

Figure 1 (A) Ideograms of the normal and inverted chromosome. (B) GTG banded partial karyotype of the patient. The normal chromosome 5 is on left and the inverted one on the right.

karyotype was interpreted as 46,XY,inv(5)(p15q11) (fig 1) and the same inversion was present in the proband's mother and maternal grandmother but not in other relatives (fig 2).

Inversion breakpoints were defined at the YAC level by fluorescence in situ hybridisation (FISH) to chromosome preparations from the proband. YACs containing chromosome 5 specific sequences from several locations on the p and q arms were selected according to the Genome Database (www.genome.wi.mit.edu/cgi-bin/conting/phys_map). YAC DNA was labelled with biotin using nick translation. The labelled probes were visualised with FITC-avidin (Vector) and the chromosomes were counterstained with DAPI (Sigma). Hybridisations were analysed with a Zeiss Axioplan epifluorescence microscope and images were captured with the Power Gene FISH System (PSI).

Breakpoints were found at YACs 956a11 (5p15.1, D5S1954-D5S416 at 28 cM from the short arm telomere) and 854b12 (5q11.2, D5S2076-D5S664 at 63 cM) (fig 3). Therefore the full karyotype of the proband was 46,XY,inv(5)(p15q11).ish inv (5)(p15.1q11.2)(D5S1954sp,D52076sp).

Segregation of the polymorphic markers D8S1385 and D8S558 closely linked to *KCNQ3* and of the Thr752Asn polymorphism located in exon 16 of the *KCNQ2* gene was studied in the family members. This study excluded linkage of BFNC to *KCNQ2* while linkage to *KCNQ3* was not excluded. Therefore, the *KCNQ3* coding region, including the exon-intron boundaries, was analysed in the patient and his mother. Polymerase chain reactions (PCR) were performed using primers and PCR conditions kindly provided by Shinichi Hisose, Department of Paediatrics, Fukouka University, Japan. PCR products were directly sequenced using ABI PRISM 310 sequencer and the Big Dye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystem, Foster City, CA). No mutations were found.

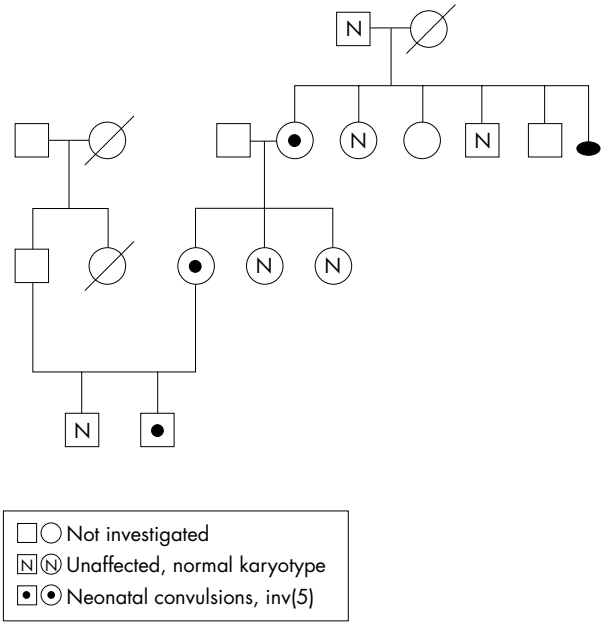

Figure 2 Family pedigree.

DISCUSSION

This report is another example of a rare case of an inherited pericentric inversion of chromosome 5 with the presence of clinical findings. Other pericentric inversions of the same region of chromosome 5 have been described,[5 6] but not with the same breakpoints in both arms. In our family, FISH analysis localised the 5p breakpoint at YAC clone 956a11 located in proximal 5p15.1 and the 5q breakpoint at YAC 854b12 located in 5q11.2. The breakpoint in the short arm of chromosome 5 in this report is not in the cri du chat syndrome critical region, mapped in 5p15.3 for high pitched cry and in 5p15.2 for the remaining features.[7] Therefore, this is the first example of a family with a pericentric inversion of chromosome 5 and BFNC.

In BFNC, seizures begin in the neonatal period and generally have a favourable outcome with spontaneous remission in the first year of life. The clinical heterogeneity of this disorder has been suggested by differences among pedigrees in the risk of developing epilepsy in later life.[8] In the last few years, two loci for BFNC have been mapped to chromosomes 20q13.3 and 8q24[1 2] showing that this disorder is also genetically heterogeneous. The majority of families are linked to chromosome 20q with mutations in the potassium channel gene *KCNQ2.* Only two families have been detected with mutations in the highly homologous gene *KCNQ3* at 8q24,[9 10] so *KCNQ2* was considered to be a major gene locus for BFNC.[3 4 9] Mutations in both genes are heterozygous, according to the autosomal dominant inheritance pattern of BFNC. A new benign idiopathic epilepsy in early life, with a favourable outcome and autosomal dominant inheritance, has been reported.[11] In this family, the seizures began between 4 and 7 months of life and for this reason the condition was called benign infantile familial convulsions (BFIC). A locus for BFIC has been mapped to chromosome 19q12-13,[12] suggesting that BFNC and BFIC are not allelic diseases with variable expressivity but are different entities. However, in the seven families with BFIC recently investigated, no evidence of linkage with chromosome 19 markers has been found.[13]

In conclusion, there are several lines of evidence for clinical and genetic heterogeneity of this condition and at least three loci responsible for autosomal dominant benign epilepsy of early life. Our family shows a strong correlation between the chromosome 5 inversion and BFNC. In fact, the disease was present only in the three inv(5) subjects but not in the two

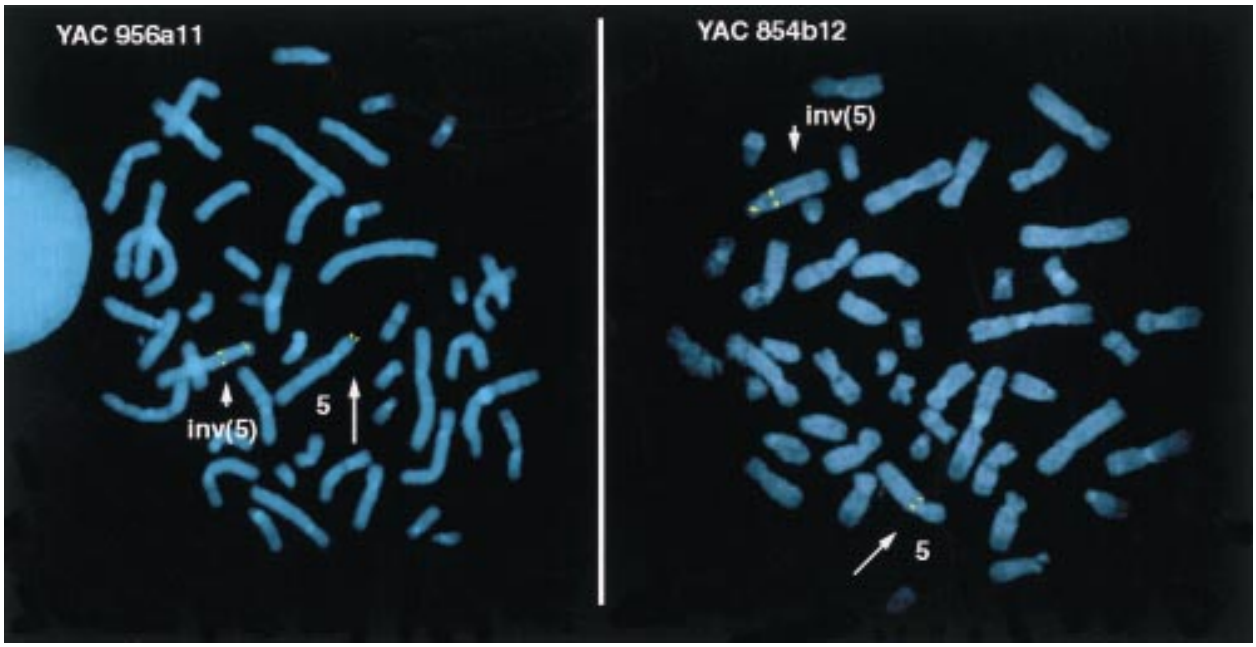

Figure 3 FISH analysis with the YAC 956a11 (left) and YAC 854b12 (right) crossing the inv(5) breakpoints on the short and long arm, respectively.

aunts of the proband or in his brother. We hypothesised that breakage or transcription silencing of a gene at one of the inversion breakpoints is responsible for the disease. Moreover, the exclusion of linkage of BFNC to *KCNQ2* and *KCNQ3* in this family supports this hypothesis.

Authors' affiliations
D Concolino, M A Iembo, P Strisciuglio, Department of Paediatrics, University of Catanzaro "Magna Graecia", Italy
E Rossi, S Giglio, Department of General Biology and Medical Genetics, University of Pavia, Italy
G Coppola, E Miraglia del Giudice, Department of Paediatrics, 2nd University of Naples, Italy

Correspondence to: Dr P Strisciuglio, Department of Paediatrics, Faculty of Medicine, University of Catanzaro, C/o Ospedale "A Pugliese", Viale Pio X, 88100 Catanzaro, Italy; Strisciuglio-unicz@libero.it

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